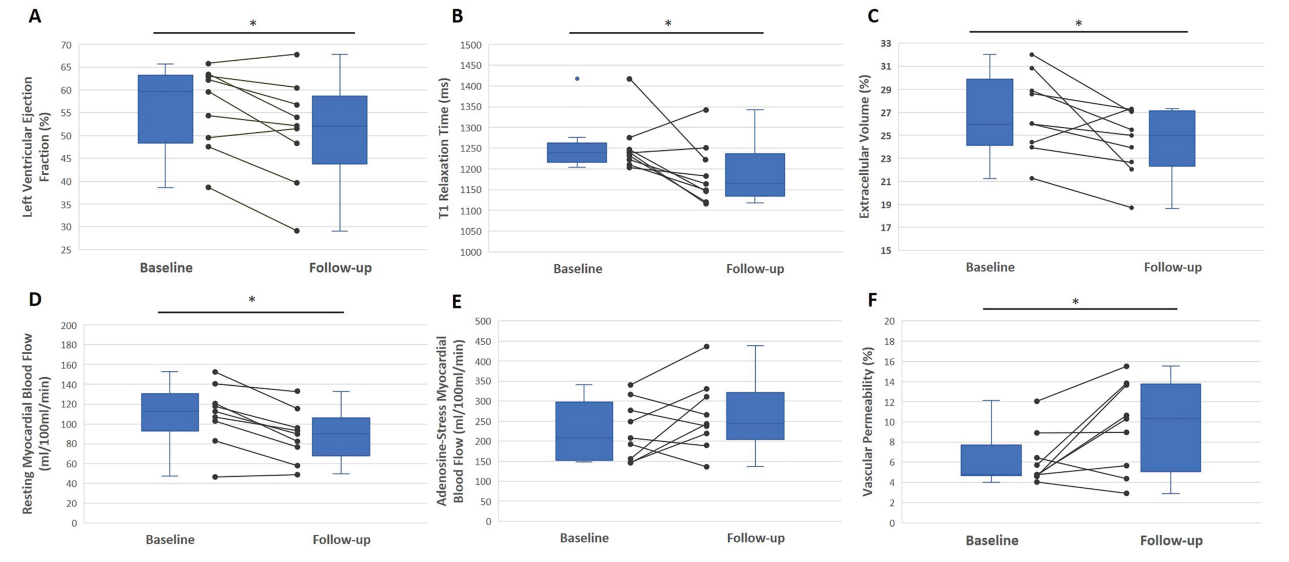

Figure 1 Changes in (*A*) left ventricular ejection fraction, (*B*) T1 relaxation time, (*C*) extracellular volume, (*D*) myocardial blood flow at rest and (*E*) stress, and (*F*) vascular permeability at rest with 4–6 weeks of vascular endothelial growth factor signalling pathway inhibitor therapy.

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References

1. Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: a population-based study. *Lancet* 2015;**385**:1206–1218.
2. Zamorano JL, Lancellotti P, Muñoz DR, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017;**19**:9–42.
3. Steeghs N, Gelderblom H, Roodt JO, Christensen O, Rajagopalan P, Hovens M, Putter H, Rabelink TJ, de Koning E. Hypertension and rarefaction during treatment with telatinib, a small molecule angiogenesis inhibitor. *Clin Cancer Res* 2008;**14**:3470–3476.
4. Narayan V, Keefe S, Haas N, Wang L, Puzanov I, Putt M, Catino A, Fang J, Agarwal N, Hyman D, Smith AM, Finkelman BS, Narayan HK, Ewer S, ElAmm C, Lenihan D, Ky B. Prospective evaluation of sunitinib-induced cardiotoxicity in patients with metastatic renal cell carcinoma. *Clin Cancer Res* 2017;**23**:3601–3609.
5. Papanastasiou G, Williams MC, Dweck MR, Mirsadraee S, Weir N, Fletcher A, Lucatelli C, Patel D, van Beek EJ, Newby DE, Semple SI. Multimodality quantitative assessments of myocardial perfusion using dynamic contrast enhanced magnetic resonance and 15 O-labeled water positron emission tomography imaging. *IEEE Trans Radiat Plasma Med Sci* 2018;**2**:259–271.

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Viral genome search in myocardium of patients with fulminant myocarditis

Fulminant myocarditis (FM) is a form of acute myocardial inflammation leading to acute-onset clinical presentation requiring inotropic and, in severe cases, mechanical circulatory support.[1] As highlighted by recent registries, FM is associated with high rates of death and heart transplant.[2,3] Endomyocardial biopsy (EMB) is the gold standard for the diagnosis of acute myocarditis and allows histologic characterization.[1,4] The role of viruses in myocarditis aetiology has been historically recognized, with parvovirus (PV) B19, adenoviruses, human herpes virus type 6 (HHV6) and enteroviruses being the most common agents identified in myocardium.[4–6] A growing body of literature indicates that viruses, particularly PVB19, may be found in a large proportion of patients who do not have myocarditis, and additional studies are needed to determine their causal role.[7] It has been stated that the presence of specific viruses in the heart may contraindicate the use of immunosuppression, particularly in lymphocytic forms, where its role is mostly controversial.[1] On the other hand, immunosuppressive therapy, even though not standardized, is the cornerstone of treatment for eosinophilic and giant-cell myocarditis, cardiac sarcoidosis, and, regardless of the underlying histology, for myocarditis related to systemic autoimmune diseases and immune checkpoint inhibitor therapy.[4] Although the latest scientific statement of the European Society of Cardiology recommends that immunosuppression should be started only after ruling out active infection on EMB by polymerase chain reaction (PCR),[4] the

Table 1 Clinical presentation, initial diagnostic findings, in-hospital management and 1-year outcome of patients admitted with histologically proven lymphocytic fulminant myocarditis comparing cases with vs. those without a polymerase chain reaction-based viral search performed in myocardium

	No. of patients with available data	Lymphocytic fulminant myocarditis ($n = 120$)		
		Viral genome search not performed ($n = 93$)	Viral genome search performed ($n = 27$)	*P*-value
Demographics				
Age, years, median (Q1–Q3)	120	38 (23–53)	34 (23–50)	0.517
Female sex, *n* (%)	120	50 (53.7)	11 (40.7)	0.278
Presenting symptoms, *n* (%)				
Dyspnoea	119	63 (68.4)	21 (77.7)	0.115
Chest pain	117	27 (30.0)	13 (48.1)	0.106
Syncope	117	19 (21.1)	2 (7.4)	0.153
Prodromal symptoms, *n* (%)	120	76 (81.7)	20 (74.0)	0.417
Autoimmune diseases, *n* (%)	115	11 (12.3)	2 (7.7)	0.729
ECG at admission, *n* (%)				
Normal	115	6 (6.8)	0 (0.0)	0.333
ST-segment elevation	115	33 (37.5)	9 (33.3)	0.820
Other ST-T segment abnormalities	115	27 (30.6)	12 (44.4)	0.245
QRS >120 ms	108	36 (43.9)	4 (15.4)	0.001
Life-threatening arrhythmias[a], *n* (%)				
Cardiac arrest	116	21 (23.6)	7 (25.9)	0.801
VT/VF	68	18 (37.5)	9 (45.0)	0.537
Advanced AV block	120	6 (6.4)	2 (7.4)	1.000
Admission laboratory tests, *n* (%)				
Increased CRP	109	72 (87.8)	19 (70.3)	0.069
Increased troponin T/I or CK-MB	114	77 (88.5)	21 (77.7)	0.204
Echocardiography at admission				
LVEF, %, median (Q1–Q3)	120	20 (15–30)	25 (20–35)	0.054
LVEDD, mm, median (Q1–Q3) (patients ≥15 years)	93	48 (43–55)	52 (46–60)	0.096
Pericardial effusion, *n* (%)	114	45 (51.7)	13 (48.1)	0.827
Immunosuppressive therapy, *n* (%)	119	54 (58.7)	17 (62.9)	0.824
Steroids		46 (50.0)	13 (48.1)	1.000
Immunoglobulin		29 (31.5)	6 (22.2)	0.473
Other		9 (9.7)	5 (18.5)	0.305
Temporary MCS devices, *n* (%)	120	64 (68.8)	13 (48.1)	0.103
IABP		53 (56.9)	9 (33.3)	
Days, median (Q1–Q3)		6 (3–9)	3 (2–12)	0.147
Only		16 (17.2)	3 (11.1)	
With other MCS		37 (39.7)	6 (22.2)	
MCS other than IABP		44 (51.6)	10 (37.0)	
1-year outcome, *n* (%)	120			
Cardiac death or HTx		30 (32.2)	7 (25.9)	0.530
HTx		5 (5.3)	3 (11.1)	
Cardiac death		25 (26.8)	4 (14.8)	
Alive		63 (67.8)	20 (74.1)	

AV, atrioventricular; CRP, C-reactive protein; ECG, electrocardiogram; HTx, heart transplant; IABP, intra-aortic balloon pump; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; Q, quartile; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]Defined as ventricular arrhythmias or cardiac arrest requiring resuscitation manoeuvres that took place during the acute phase of the disease.

need to search for viral genome by PCR in the setting of FM patients is debatable and its real clinical value remains unclear. In addition, the relative frequency with which viral genome PCR on EMB is being performed in FM has not been reported previously. We thus aimed to characterize the extent of use of PCR-based viral genome search in a large cohort of histologically proven FM patients, mostly focusing on lymphocytic FM.

Data were derived from a retrospective, international, multicentre cohort study. A detailed description of the organization of the international registry on acute myocarditis has been published elsewhere.[2] In brief,

data were collected from patients seen at 16 tertiary hospitals [13 (81.3%) with heart transplant programmes] across the United States ($n = 3$), Europe ($n = 9$), and Japan ($n = 4$) with histologically proven acute myocarditis (onset of symptoms <30 days), all presenting with left ventricular systolic dysfunction (data collection period from January 2001 to March 2018). Data on nested PCR performed in myocardial tissue for the detection of cardiotropic viruses, including enteroviruses, PVB19, adenoviruses, cytomegalovirus, Epstein–Barr virus, and HHV6, were collected.

The study population included 220 patients (FM 165, non-FM 55), of whom 141 were from Europe (64%), 35 from the United States (16%), and 44 from Japan (20%). Among patients with FM, lymphocytic myocarditis was diagnosed in 120, giant-cell myocarditis in 24, eosinophilic myocarditis in 19, and cardiac sarcoidosis in 2. Myocardium PCR-based viral search was performed in 33 FM patients (20%). The use of PCR-based viral genome detection was higher in Europe (34%), compared to United States (17%) and Japan (3%). Viral search was performed in 6/45 non-lymphocytic FM patients (13%), yielding positive results in one patient (17%) with Epstein–Barr virus and eosinophilic FM. Among patients with lymphocytic FM, 27 (22%) had a PCR-based viral genome search performed, yielding positive results in five patients (18%), with PVB19 identified in all positive cases. Three cases had low viral titres of myocardial PVB19 genome equivalents per microgram of isolated nucleic acids, one case had high titre and in one case titre was not reported; two cases were treated with intravenous immunoglobulin. When comparing lymphocytic FM patients with and without a myocardium PCR-based viral search performed (*Table 1*), there were no statistically significant differences in demographics, early management, including prevalence of use of immunosuppressive therapy, and 1-year outcome.

Viral genome search was performed in 22% of lymphocytic FM patients, with PVB19 being the only detected virus in all five positive cases. This is consistent with previous findings from cohorts of myocarditis patients, although not specifically addressing FM, where PVB19 was the most frequently identified virus.[5] Of note, recent evidence suggests that immunosuppression does not seem to aggravate PVB19 replication in myocardium of patients with inflammatory cardiomyopathy and PVB19 persistence.[8] Available literature on the role of myocarditis management based on viral genome identification has been mostly derived from small studies in patients affected by chronic myocarditis or inflammatory dilated cardiomyopathy and the results obtained have been inconsistent. Our survey is limited by its retrospective nature, a relatively small sample size, the lack of systematic viral genome search in the whole cohort, and the presence of heterogeneity in the techniques used for viral search analysis, based on local standards. Notwithstanding this, it provides unique information about the frequency of use of PCR-based viral genome identification in myocardium of FM patients. Whether a routine viral genome search in myocardial tissue, a time-consuming procedure, improves patient management guiding immunosuppression therapy in patients with FM remains to be proven. In acute myocarditis, especially in FM, where early immunosuppression may be crucial, initiation of immunosuppressive treatment (e.g. pulse steroid therapy) before obtaining PCR results might represent a reasonable approach. Decisions on cessation or implementation of a tailored immunosuppression may be procrastinated after final histopathological characterization and eventual virus detection. Large prospective studies are warranted to address the role of viral genome identification in acute and fulminant myocarditis.

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References

1. Tschope C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. *Circ Res* 2019;**124**:1568–1583.
2. Ammirati E, Veronese G, Brambatti M, Merlo M, Cipriani M, Potena L, Sormani P, Aoki T, Sugimura K, Sawamura A, Okumura T, Pinney S, Hong K, Shah P, Braun O, Van de Heyning CM, Montero S, Petrella D, Huang F, Schmidt M, Raineri C, Lala A, Varrenti M, Foa A, Leone O, Gentile P, Artico J, Agostini V, Patel R, Garascia A, Van Craenenbroeck EM, Hirose K, Isotani A, Murohara T, Arita Y, Sionis A, Fabris E, Hashem S, Garcia-Hernando V, Oliva F, Greenberg B, Shimokawa H, Sinagra G, Adler ED, Frigerio M, Camici PG. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2019;**74**:299–311.
3. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, Petrella D, Garascia A, Pedrotti P, Roghi A, Bonacina E, Moreo A, Bottiroli M, Gagliardone MP, Mondino M, Ghio S, Totaro R, Turazza

FM, Russo CF, Oliva F, Camici PG, Frigerio M. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. *Circulation* 2017;**136**:529–545.
4. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:2636–2648.
5. Van Linthout S, Tschöpe C. Viral myocarditis: a prime example for endomyocardial biopsy-guided diagnosis and therapy. *Curr Opin Cardiol* 2018;**33**:325–333.
6. Kindermann I, Kindermann M, Kandolf R, Klingel K, Bultmann B, Muller T, Lindinger A, Bohm M. Predictors of outcome in patients with suspected myocarditis. *Circulation* 2008;**118**:639–648.
7. Verdonschot J, Hazebroek M, Merken J, Debing Y, Dennert R, Brunner-La Rocca HP, Heymans S. Relevance of cardiac parvovirus B19 in myocarditis and dilated cardiomyopathy: review of the literature. *Eur J Heart Fail* 2016;**18**:1430–1441.
8. Tschöpe C, Elsanhoury A, Schlieker S, Van Linthout S, Kühl U. Immunosuppression in inflammatory cardiomyopathy and parvovirus B19 persistence. *Eur J Heart Fail* 2019;**21**:1468–1469.

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Acute inflammatory cardiomyopathy: apparent neutral prognostic impact of immunosuppressive therapy

The real efficacy and indication of immunosuppressive therapy (IST) in acute (i.e. <6 months) inflammatory cardiomyopathy (IC) due to lymphocytic myocarditis remain debated. Available data are controversial because they are derived from trials on chronic IC[1–3] or investigating immunomodulation in chronic viral cardiomyopathy,[4] or from observational studies including acute and chronic IC patients with short-term follow-up.[5] The aim of this study was to assess the prognostic impact of IST in a population of acute IC patients.

Methods

We analysed retrospectively all patients with acute (i.e. <6 months) left ventricular systolic dysfunction and an indication for endomyocardial biopsy (EMB) consecutively admitted at the Cardiovascular Department of Trieste, Italy, between 2000 and 2018. According to recent international statements,[6] the indications for EMB and potentional use in IC include: (i) unexplained heart failure with left ventricular ejection fration (LVEF) <40%, refractory to conventional treatment in the short term; (ii) unexplained major ventricular arrhythmias (MVAs) associated with LVEF <50%. Inflammatory cardiomyopathy was defined as the presence of EMB-proven myocarditis with LVEF <50%.[2] IST consisted of prednisone (50 mg/m^2/day with progressive

Table 1 Characteristics of inflammatory cardiomyopathy patients treated and not treated with immunosuppressive therapy

	Total (n = 65)	IST (n = 34, 52.3%)	No IST (n = 31, 47.7%)	P-value
Age (years)	46 ± 17	46 ± 19	46 ± 14	0.859
Male sex	36 (55.4)	20 (58.8)	16 (51.6)	0.559
Duration of symptoms (days)	58 [20–140]	58 [23–175]	55 [18–115]	0.451
Admission SBP (mmHg)	112 ± 18	110 ± 15	115 ± 20	0.549
NYHA class				
II	17 (26.2)	7 (20.6)	10 (32.3)	0.219
III	16 (24.6)	10 (29.4)	6 (19.4)	0.397
IV	12 (18.5)	9 (26.5)	3 (9.7)	0.093
Fulminant form	7 (10.8)	5 (14.7)	2 (6.5)	0.638
Presentation with HF	37 (56.9)	24 (70.6)	13 (41.9)	0.016
Atrial fibrillation	2 (3.1)	0 (0)	2 (6.5)	0.196
QRS length (ms)	103 ± 31	98 ± 30	109 ± 31	0.273
LVEDVi (mL/m^2)	83 ± 25	84 ± 22	82 ± 27	0.733
Baseline LVEF (%)	30 ± 9	29 ± 7	31 ± 11	0.554
LVEF at discharge (%)	34 ± 10	33 ± 8	34 ± 11	0.723
LAESAi (cm^2/m^2)	14 ± 4	14 ± 4	14 ± 5	0.823
RVD	18 (27.7)	8 (23.5)	10 (32.3)	0.515
Moderate to severe MR	20 (30.7)	10 (29.4)	10 (32.3)	0.666
RFP	22 (33.8)	10 (29.4)	12 (38.7)	0.643
Poor lymphocytic infiltrate	48 (73.8)	17 (50)	31 (100)	<0.001
Moderate to severe fibrosis at EMB	40 (61.5)	19 (55.9)	21 (67.7)	0.337
PCR virus-positive at EMB	13 (20)	6 (17.6)	7 (22.6)	0.166
Beta-blockers at discharge	55 (84.6)	28 (82.4)	27 (87.1)	0.962
ACEi/ARBs at discharge	59 (90.8)	31 (91.2)	28 (90.3)	0.286
Aldosterone receptor antagonists at discharge	34 (52.3)	18 (27.7)	16 (51.6)	0.818
Diuretics at discharge	45 (69.2)	24 (70.6)	21 (67.7)	0.524
LVRR at 24 months	31 (67.4)	19 (70.4)	12 (63.2)	0.607

Values are expressed as mean ± standard deviation, *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; EMB, endomyocardial biopsy; HF, heart failure; IST, immunosuppressive therapy; LAESAi, left atrial end-systolic area index; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodelling; MR, mitral regurgitation; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PCR, polymerase chain reaction; RFP, restrictive filling pattern; RVD, right ventricular dysfunction; SBP, systolic blood pressure.